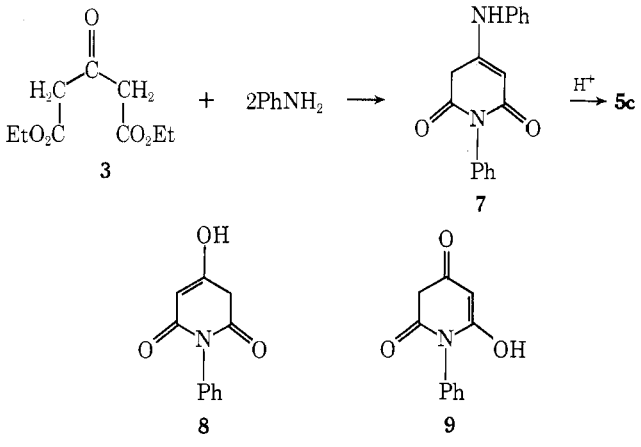

Experimental Section

3-Oxoglutaranilic Acid (1). A solution of 1.88 g (0.02 mol) of aniline in 20 ml of anhydrous ether was added at a slow drop rate to a stirred suspension of 2.56 g (0.02 mol) of 3-oxoglutaric anhydride in 20 ml of the same solvent. After the addition was complete, the mixture was stirred for a further 2 hr. The resulting solid was collected and washed with anhydrous ether to give 3.80 g (86%) of a white powder: mp 105–106°; ir (KBr) 3300, 1730, and 1660 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.4. Found: C, 59.9; H, 5.0; N, 6.5.

Decarboxylation of 1. Compound 1 (0.5 g, 0.0023 mol) was heated at 120° for 5 min, as CO_2 was evolved. On cooling, the reaction mixture solidified to give 0.40 g (100%) of **2**: mp (benzene) 84–85°, undepressed on admixture with an authentic sample; ir (KBr) identical with that of an authentic sample.

Reaction of Phenyl Isocyanate with 3. Sodium (2.3 g, 0.1 mol) was added to a solution of 20.2 g (0.1 mol) of diethyl 3-oxoglutarate in 120 ml of anhydrous ether and the mixture was warmed gently until all the sodium had dissolved. The resulting solution was stirred at 0–5° as 11.9 g (0.1 mol) of phenyl isocyanate was added dropwise. The suspension thus obtained was heated at reflux temperature on a steam bath for 2 hr. After cooling, 500 ml of water was added and the mixture was stirred until all the solid had dissolved. The aqueous layer was separated and acidified with 5 *N* HCl, and the precipitated solid was collected and washed with water. Extraction of the solid with 300 ml of benzene, followed by evaporation of the solvent, yielded 0.75 g of **6**. An analytical sample, obtained by recrystallization from ethanol, decomposed on heating, with no clearly defined melting point: mass spectrum *m/e* (rel intensity) 394 (29), 348 (27), 322 (4), 302 (11), 256 (38), 174 (5), 120 (12), 119 (5), 93 (100), 77 (8).

Anal. Calcd for $C_{21}H_{18}N_2O_6$: C, 64.0; H, 4.6; N, 7.1. Found: C, 63.7; H, 4.5; N, 6.8.

The undissolved material was again washed with benzene to give crude **5b**, 10.8 g (39%): mp (EtOH) 198–200°, undepressed by admixture with an authentic sample;[7] ir (KBr) identical with that of an authentic sample.

4-Anilino-1-phenyl-2,6(1*H*,3*H*)-pyridinedione (7). This compound was prepared by the following modification of the method described by Emery.[6] A mixture of 40.1 g (0.2 mol) of diethyl 3-oxoglutarate and 37.2 g (0.4 mol) of aniline was heated at 120° for 4 hr in an open flask. After it had cooled, a vacuum distillation apparatus was attached and a pressure of about 50 mm was maintained as the bath temperature was raised to 180° over a 30-min period. The reaction was completed by heating for a further 1.5 hr at 180° under reduced pressure. After cooling, the reaction mixture was warmed with 100 ml of ethanol to obtain a suspension of yellow solid, which was filtered from the hot mixture. The solid was dissolved in a solution of 16 g of sodium hydroxide in 400 ml of 50% methanol. After filtration, the solution was acidified with acetic acid to obtain 6.7 g (12%) of **7**: mp (DMF–methanol) 281–283° dec (lit.[6] mp 275° dec); NMR (DMSO-d_6) δ 9.20 (s, 1), 7.0–7.6 (m, 10), 5.45 (s, 1), 3.81 (s, 2).

1-Phenylpiperidine-2,4,6-trione (5c). Compound 7 (5 g, 0.018 mol) was added to a boiling mixture of 50 ml of 50% acetic acid and 5 ml of concentrated HCl. The mixture was heated at reflux temperature for 5 min and a small amount of undissolved solid was removed by filtration of the hot mixture. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 35 ml of water, and the solution was made basic by dropwise addition of 40% KOH. After extraction with ether (2 × 10 ml), the aqueous solution was acidified with acetic acid and the small amount of precipitated solid was removed by filtration. The solution was acidified to pH 3–4 with concentrated HCl and chilled, and the precipitated solid was collected. The yield of crude **5c** was 2.0 g (55%): mp (CH_3CN) 183–184° dec; ir (KBr) 3110 (broad), 1711, 1670, 1640, 1370, 1255, 1208, 841, and 700 cm^{-1}; NMR (DMSO-d_6) δ 17.1 (broad s, 1), 7.0–7.6 (m, 5), 5.42 (s, 1), 3.65 (s, 2); mass spectrum *m/e* (rel intensity) 203 (55), 175 (18), 119 (100), 93 (38), 91 (37), 84 (55), 77 (9), 64 (19), 63 (10), 51 (11), 42 (21), 39 (12).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9. Found: C, 64.6; H, 4.6; N, 7.2.

Registry No.—**1**, 55267-57-7; **2**, 102-01-2; **3**, 105-50-0; **5b**, 55267-58-8; **5c**, 55267-59-9; **6**, 55267-60-2; **7**, 55267-61-3; 3-oxoglutaric anhydride, 10521-08-1; phenyl isocyanate, 103-71-9.

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Bufadienolides. 30. Synthesis of the Ch'an Su Component 15β-Hydroxybufalin[1,2]

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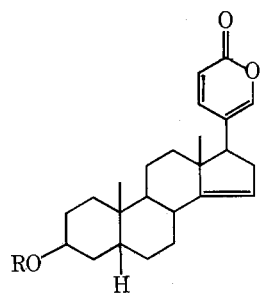
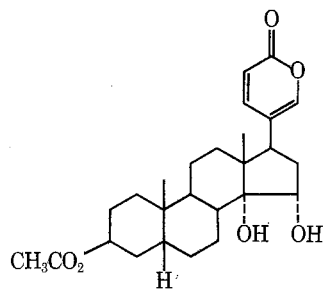
Received January 13, 1975

Venom from the toad *Bufo bufo gargarizans* is generally employed to prepare the Chinese medicinal preparation, Ch'an Su.[4] The first bufadienolide component was isolated from Ch'an Su some 63 years ago,[5] and a number of later investigations produced most of the bufadienolides now considered representative of toad venoms. In a recent continuation of their very careful toad venom isolation studies the Meyer group[6] has succeeded in isolating 11 new bufadienolides from Ch'an Su. One of these new bufadienolides was found to be 15β-hydroxybufalin (**3d**). The structure of the substance was determined by instrumental methods and comparison with the higher melting cis diol obtained by osmium tetroxide hydroxylation of 14-dehydrobufalin acetate (**1a**). The mixture of diols **2** and **3a** obtained by this procedure amounted to a 10% yield. Interestingly, the β-cis glycol was obtained in about 2% yield.

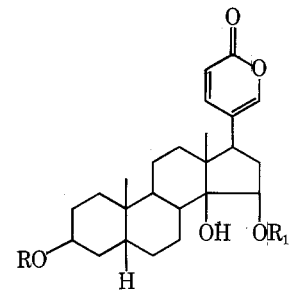
Since 15β-hydroxybufalin may be a component of other toad venoms and possess potentially useful biological properties, we have developed a new synthesis of this substance based on our prior route to 15β-hydroxy digitoxigenin.[7] To begin with, we subjected 14-dehydrobufalin acetate to a modified osmium tetroxide hydroxylation procedure. By this means, α-cis diol **2** was obtained in up to 28% yield and β-cis diol **3a** was isolated in about 5% yield. The most efficient route to the β-cis diol was realized using a Woodward cis-hydroxylation procedure.[7] Treatment of 14-dehydrobufalin (**1b**) or its 3-acetate derivative **1a** with iodine and silver acetate led to 21% yields of 15β-acetate **3b** and **3c**. Next, an acid-catalyzed hydrolysis procedure was utilized to convert the acetate derivatives **3a–c** to 15β-hydroxybufalin (**3d**). By this approach yields of triol **3d** ranged from



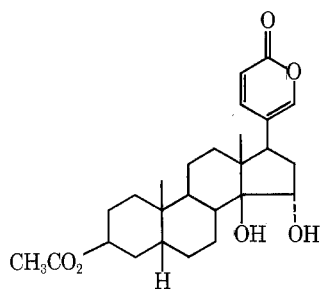
1a, $R_1 = COCH_3$
b, R = H



2



3a, $R = COCH_3$; $R_1 = H$
b, R = H; $R_1 = COCH_3$
c, $R = R_1 = COCH_3$
d, R = R_1 = H



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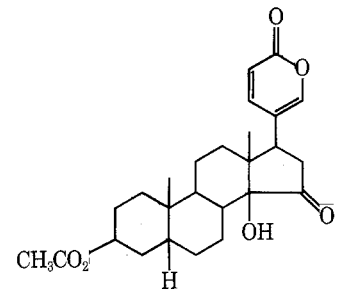
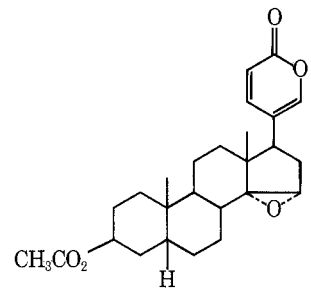


4



6

about 30% starting with diacetate **3c** to over 50% starting with monoacetate **3a.**

Additional evidence for the structure assigned to 15β-hydroxybufalin (**3d**) was obtained by oxidizing 3β-acetate **3a** to 15-ketone **4.**[8] As part of an earlier study we synthesized 15α-hydroxybufalin from 14-dehydrobufalin acetate (**1a**) and by oxidation of the 15α-alcohol obtained 15-ketone **4.** The specimens of 15-ketone **4** obtained from the 15β- and 15α-alcohols **3a** and **5** were identical. The same 15-ketone (**4**) was more conveniently obtained by chromium trioxide oxidation of α-epoxide **6,** as previously reported.[8]

In summary, the Woodward cis-hydroxylation approach to 15β-hydroxybufalin has provided a workable means of obtaining the substance for biological evaluation. The route from 14-dehydrobufalin (**1b**) also completes a formal total synthesis[9] of this rare toad venom constituent.

Experimental Section

A summary of equipment, chromatographic substrates, and general techniques has been provided in the introduction to the Experimental Section of Part 23.[10] Bufalin employed as starting material for preparation of 14-dehydrobufalin was isolated from the Chinese medicinal preparation Ch'an Su. The mutual identity of all comparison specimens was established by mixture melting point and infrared spectral and TLC determination.

The purity of each specimen was ascertained by thin layer chromatography on silica gel (E. Merck, Darmstadt) using 3:3:4 acetone–chloroform–hexane as solvent.

3β-Acetoxy-14α,15α-dihydroxy-5β-bufa-20,22-dienolide (2) and 3β-Acetoxy-14β,15β-dihydroxy-5β-bufa-20,22-dienolide (3a). Selective hydroxylation of 14-dehydrobufalin acetate (**1a,** 0.6 g) was performed in dry ethyl ether (120 ml)–pyridine (12 ml) with osmium tetroxide (0.6 g) at 10° over 12 hr as previously described employing 14-dehydrodigitoxigenin.[7] The crude product was chromatographed on a column of silica gel. The fraction eluted with 3:1 hexane–acetone weighed 0.25 g and corresponded to a mixture of diols **2** and **3a.** Careful rechromatography using the same solvent gave 0.172 g (mp 225–237°) of α-diol **2** as prisms from chloroform–hexane and 0.033 g of β-diol **3a** (mp 275–279°) as prisms from chloroform–hexane.

The preceding experiment was repeated using 0.3 g of 14-dehydrobufalin acetate (**1a**) and 0.3 g of osmium tetroxide. After diluting the reaction mixture with methanol (40 ml) the resulting solution was treated with hydrogen sulfide.[11] The osmium sulfides were removed by filtration and evaporation of the solvent afforded a 0.28-g residue which was purified as described above. By this means, 0.075 g (mp 222–235°) of α-diol **2** and 0.016 g (271–278°) of β-diol **3a** was obtained. Melting points of 170–240° for α-diol **2** and 273–277° for β-diol **3a** have been reported.[6]

An analytical sample of α-diol **2** exhibited ir ν_{max} (KBr) 3560, 3440 (OH), 1740 (ester CO), 1712, 1700, 1680 (conjugated CO), 1637, 1540 (conjugated C=C), 1244, 1215 (ester C–O), 1135, 1033, 954, 904, 835, 748 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.72 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 2.03 (3 H, s, 3-$OCOCH_3$), 4.28 (1 H, broad t, J = 7.5 Hz, 15-H), 5.02 (1 H, broad peak, 3α-H), 6.18 (1 H, d, J = 9.5 Hz, 23-H), 7.27 (1 H, d, J = 2.5 Hz, 21-H), and 7.90 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.36; H, 8.13.

A pure sample of β-diol **3a** displayed ir ν_{max} (KBr) 3580, 3450 (OH), 1740 (ester CO), 1713, 1700, 1690 (conjugated CO), 1638, 1540 (conjugated C=C), 1244, 1215 (ester C–O), 1135, 1035, 955, 905, 837, 748 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.70 (3 H, s, 18-CH_3), 0.92 (3 H, s, 19-CH_3), 2.04 (1 H, s, 3-$OCOCH_3$), 4.27 (1 H, broad t, J = 7.5 Hz, 15α-H), 5.06 (1 H, broad peak, 3α-H), 6.26 (1 H, d, J = 9.5 Hz, 23-H), 7.23 (1 H, d, J = 3 Hz, 21-H), and 7.65 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.49; H, 8.17.

15β-Acetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (15β-Acetoxybufalin, 3b). To a solution of 14-dehydrobufalin (**1b,** 0.3 g) in acetic acid (72 ml)–water (3.6 ml) was added iodine (2.4 g) and silver acetate (2.4 g). The mixture was stirred at room temperature for 24 hr and the solution was filtered. The solvent was evaporated and the yellow residual solid was chromatographed on a column of silica gel. The fraction eluted by hexane–acetone (3:1) was recrystallized from acetone–hexane to afford 0.252 g (21%) of 15β-acetoxy-β-diol **3b** as prisms melting at 213–216°: TLC R_f 0.23 (light blue color with sulfuric acid); uv λ_{max} (MeOH) 297.5 nm (log ϵ 3.24); ir ν_{max} (KBr) 3460, 3430 (OH), 1760 (ester CO), 1710, 1700, 1698 (conjugated CO), 1636, 1540 (conjugated C=C), 1258, 1244, 1214 (ester C–O), 1135, 1045, 1033, 1007, 953, 938, 903, 834, 800, 747 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.75 (3 H, s, 18-CH_3), 0.93 (3 H, s, 19-CH_3), 2.09 (3 H, s, 15-OAc), 4.10 (1 H, broad s, 3α-H), 5.56 (1 H, t, J = 7.5 Hz, 15α-H), 6.25 (1 H, d, J = 9.5 Hz, 23-H), 7.24 (1 H, d, J = 2.5 Hz, 21-H), 7.86 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 (M^+ – AcOH).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.13.

A 0.474-g amount of unreacted starting material was also isolated accompanied by 0.418 g of an amorphous substance which was not identified.

3β,15β-Diacetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (15β-Acetoxybufalin Acetate, 3c). Method A. From 14-Dehydrobufalin Acetate (1a). Olefin **1a** (0.6 g) in acetic acid (36 ml)–water (1.8 ml) was allowed to react with iodine (1.3 g) and silver acetate (1.3 g) as described for the Woodward cis hydroxylation of 14-dehydrobufalin (**1b**). Chromatography of the crude product on silica gel and elution with 5:1 hexane–acetone yielded 0.123 g (20.5%) of diacetate **3c** as an amorphous solid: TLC R_f 0.37 (green to light blue color with sulfuric acid); uv λ_{max} (EtOH) 297 nm (log ϵ 3.22); ir ν_{max} (KBr) 3420 (OH), 1755 (ester CO), 1740–1710 (ester CO and conjugated CO), 1635, 1537 (conjugated C=C), 1260, 1250, 1240, 1230 (ester CO), 1120, 1025, 950, 830, 790, 750 cm^{-1}; NMR (10% solution in $CDCl_3$) δ 0.76 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 2.03 (3 H, s, 3-OAc), 2.11 (3 H, s, 15-OAc), 5.02 (1 H, broad peak, 3α-H), 5.54 (1 H, broad t, 15α-H), 6.27 (1 H, d, J = 9.5 Hz, 23-H), 7.22 (1 H, d, J = 2.5 Hz, 21-H), 7.84 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H); mass spectrum m/e 486 (M^+), 468 ($M^+ - H_2O$), 426 (M^+ – AcOH), 408 ($M^+ - H_2O$ – AcOH), 348 (M^+ – 2AcOH).

Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.37; H, 7.91.

In addition to 15β-acetate **3c**, a 0.231-g amount of unreacted starting material was recovered.

Method B. From 15β-Hydroxybufalin Acetate (3a). A 0.05-g sample of acetate **3a** was acetylated with acetic anhydride (0.7 ml)–pyridine (1.2 ml) at room temperature over 18 hr. The crude product (0.06 g) was purified as described in method A to afford 0.043 g (86%) of diacetate **3c** identical with the specimen obtained by method A.

Method C. From 15β-Acetoxybufalin (3b). Acetylation of acetate **3b** (0.06 g) was conducted as described in method B above and 0.041 g (84%) of diacetate **3c** was isolated and found identical with the product of method A.

15β-Hydroxybufalin (3β,14β,15β-Trihydroxy-5β-bufa-20,22-dienolide, 3d). Method A. From 15β-Hydroxybufalin 3-Acetate (3a). A solution of 3β-acetate **3a** (0.059 g) in 80% ethyl alcohol (33 ml) containing sulfuric acid (0.22 ml) was allowed to remain at room temperature for 5 days. The solution was poured into water, neutralized with dilute sodium bicarbonate, and extracted with chloroform and the combined extract was washed with water. After removal of solvent the residue (0.05 g) was chromatographed on a column of silica gel and the fractions eluted with 3:1 to 2:1 hexane–acetone were recrystallized from acetone–hexane to provide 0.032 g of 15β-hydroxybufalin melting at 267–269° (lit.[6] mp 266–269°) as needles: TLC R_f 0.15 (light blue color with sulfuric acid); uv λ_{max} (MeOH) 297.5 nm (log ϵ 3.23); ir ν_{max} (KBr) 3460, 3428 (OH), 1720, 1700 (conjugated CO), 1635, 1540 (conjugated C=C), 1130, 1040, 1030, 950, 835, 745 cm^{-1}; NMR (10% solution of $CDCl_3$) δ 0.71 (3 H, s, 18-CH_3), 0.91 (3 H, s, 19-CH_3), 4.11 (1 H, broad peak, 3α-H), 4.26 (1 H, broad peak, 15α-H), 6.27 (1 H, d, J = 9.5 Hz, 23-H), 7.22 (1 H, d, J = 2.5 Hz, 21-H), 7.83 (1 H, dd, J = 9.5 and 2.5 Hz, 22-H), mass spectrum m/e 402 (M^+), 384 ($M^+ - H_2O$), 366 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.55; H, 8.48.

Method B. From 15β-Acetoxybufalin (3b). The preceding experiment was repeated employing 15β-acetate **3b** (0.05 g) in 80% methyl alcohol (60 ml) containing 0.2 ml of 35% hydrochloric acid. The product was purified to yield 15β-hydroxybufalin weighing 0.019 g and melting at 265–268°.

Method C. From 15β-Acetoxybufalin Acetate (3c). The acid hydrolysis reaction of method A was applied to diacetate **3c** (0.025 g) using 30 ml of either 80% ethyl alcohol or methyl alcohol containing sulfuric acid (0.1 ml). In this experiment the 15β-hydroxybufalin (0.008 g, mp 263–267°) was isolated by preparative thin layer chromatography.

The specimens of 15β-hydroxybufalin (**3b**) obtained by means of methods A–C were found to be identical.

3β-Acetoxy-14β-hydroxy-15-oxo-5β-bufa-20,22-dienolide (4). A solution of 15β-hydroxybufalin 3-acetate (**3a**, 0.075 g) in acetic acid (1.5 ml) was treated with a solution of chromium trioxide (0.028 g) in acetic acid (0.5 ml)–water (0.03 ml). After 1.5 hr, stirring was discontinued and 3.5 hr later methyl alcohol (0.3 ml) was added. The mixture was poured into ice–water and extracted with chloroform and the combined extract was washed with water. Solvent was removed and the residue (0.077 g) was chromatographed on a column of silica gel. Elution with 6:1 hexane–acetone and recrystallization of this fraction from acetone led to 0.049 g of 15-ketone **4** as needles melting at 259–261°. The ketone **4** was identical with specimens obtained by analogous oxidation of trans diol **5** and α-epoxide **6**.[8]

Registry No.—**1a**, 22612-50-6; **1b**, 7439-77-2; **2**, 39844-84-3; **3a**, 39844-82-1; **3b**, 55156-32-6; **3c**, 39844-83-2; **3d**, 39844-81-0; **4**, 31444-12-9; osmium trioxide, 20816-12-0; silver acetate, 563-63-3; acetic anhydride, 108-24-7; chromium trioxide, 1333-82-0.

References and Notes

(1) Part 93 of the series, Steroids and Related Natural Products. For Part 92 refer to Y. Kamano, G. R. Pettit, and M. Tozawa, *J. Chem. Soc.*, in press. For Part 29 of the bufadienolide series, see Y. Kamano, G. R. Pettit, and M. Inoue, *J. Org. Chem.*, **39**, 3007 (1974).

(2) We are pleased to acknowledge support of this investigation by the National Cancer Institute, National Institutes of Health (performed pursuant to Contract N01-CM-12308 with the Division of Cancer Treatment, NCI, Department of Health, Education and Welfare), the J. W. Kieckhefer Foundation, and the Fannie E. Rippel Foundation.

(3) (a) Department of Chemistry, School of Medicine, Premedical Course, The Jikei University, Kokuryomachi, Chofushi, Tokyo, 182, Japan; (b) Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Fukazawa, Setagayaku, Tokyo 158, Japan.

(4) On a recent visit to the People's Republic of China one of us (GRP) saw specimens of *Bufo bufo gargarizans* prominently displayed in medical collections and learned of current applications of Ch'an Su in traditional medical treatment, particularly for its anesthetic, cardiac, and antiinflammatory effects. These interesting observations were made while a member of the National Academy of Sciences Pharmacology Delegation to the People's Republic of China, June 1974.

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A New Method for the Dehydration of Nitro Alcohols

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Received February 26, 1975

While synthesizing a variety of nitro compounds for use in connection with our recent study of nitro group reduction by titanous ion,[1] we attempted to prepare several nitroolefins by dehydration of the corresponding 2-nitro alcohols. These nitro alcohols are, of course, readily available by aldol-type addition of nitroalkanes to aldehydes and ketones.[2,3] A search of the literature reveals that, although a number of methods have been employed using such reagents as phosphorus pentoxide[4] and phthalic anhydride,[5] such dehydrations are normally carried out by first acetylating the hydroxyl and then effecting elimination with sodium acetate.[6] In our experience, however, yields obtained using this method were low and variable, perhaps because of the severe reaction conditions (5 hr, 120°). We have therefore devised a new, mild method of dehydration which we wish to report here.

We reasoned that the key to effecting dehydration lay simply in transforming the hydroxyl into a better leaving group, and we therefore treated the representative nitro alcohol, 2-nitro-3-pentanol, with 1 equiv of methanesulfonyl chloride in methylene chloride at 0°.[7] After addition of triethylamine and stirring for 15 min at 0°, 2-nitro-2-pentene could be isolated in 80% yield.[8]

Some of our results are given in Table I.